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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,767	08/07/2006	J. David Schaffer	PHUS040120US3	3848

38107 7590 08/17/2010

PHILIPS INTELLECTUAL PROPERTY & STANDARDS
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EXAMINER	
WHALEY, PABLO S	
ART UNIT	PAPER NUMBER
1631	
MAIL DATE	DELIVERY MODE
08/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,767	SCHAFFER ET AL.	
	Examiner	Art Unit	
	PABLO WHALEY	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3,4,7,8,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,9-21 and 24-26* is/are rejected.

7)☒ Claim(s) *12 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/2006; 8/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. The restriction requirement between Group I and Group II, as set forth on pages 2 and 3 of the Office action mailed 3/31/2010, is withdrawn after further consideration of applicant's remarks. Applicant's election with traverse of Species (iv), as recited claim 9, directed to species of genetically evolved genes, in the reply filed on 04/28/2010 is acknowledged. However, to clarify the record, the disclosed species actually lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

Species A: The following claims disclose different species with respect to the genus of genes:

(i) generating offspring chromosomes by mating selected parent chromosomes of the-present chromosome population, each offspring chromosome having an expressed sub-set- size gene value within a range defined by expressed sub-set-size gene values of the parent chromosomes from which that offspring chromosome is generated, as in claim 3.

(ii) generating offspring chromosomes having (i) values of genes other than the expressed sub- set-size gene selected from a group consisting of the set of values of genes of the parent chromosomes other than the expressed sub-set-size genes of the: parent chromosomes, and (ii) a value of the expressed sub-set-size gene selected within a range defined by the expressed sub-set-size gene values of the parent chromosomes, as in claim 7.

(iii) each offspring chromosome being generated from two parent chromosomes of the present chromosome population by: (i) filling genes of the offspring chromosome with gene values common to both parent chromosomes and (ii) filling remaining genes with gene values that are unique to one or the other of the parent chromosomes; and selectively mutating genes values of the offspring chromosomes that are unique to one or the other of the parent chromosomes without mutating gene values of the offspring chromosomes that are common to both parent chromosomes, as in claim 8.

(iv) generating offspring chromosomes from selected combinations of chromosomes of the present generation chromosome population; and replacing a selected chromosome of the present generation chromosome population with a selected offspring chromosome if either: (i) the selected offspring chromosome is more fit than the selected chromosome of the present generation chromosome population, or (ii) the selected offspring chromosome is as fit as the selected chromosome of the present generation chromosome population and the selected offspring chromosome has fewer expressed genes than the selected chromosome of the present generation chromosome population, as in claim 9.

The above species do not relate to a single-inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Regarding Species A, the technical feature linking the species appears to be generating offspring. However, the claims encompass different special technical features directed to generating offspring chromosomes based on values of genes of an expressed sub-set-size gene

within a range defined by parent chromosomes, which are no so linked by methods that generate offspring based on combination replacement or methods based on fitness.

Accordingly, the disclosed species are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

Applicant's arguments that species i, ii, iii, and iv are not mutually exclusive have been fully considered but are not persuasive for at least the following reasons. Namely, generating offspring chromosomes based on values within a range is divergent from methods that generate offspring based on filling genes with common values, and replacement based on fitness. Claims 3, 4, 7, 8, 22, and 23 are hereby withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 1-26 are pending. Claims 3, 4, 7, 8, 22, and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 1, 2, 5, 6, 9-21, and 24-26 are under consideration.

Drawings

Drawings filed 08/07/2006 have been accepted.

Information Disclosure Statement

The information disclosure statement filed 10/11/2006 has been considered in full.

The information disclosure statement filed 08/07/2006 has been considered in full.

Objections

Claim 12 is objected to because of the following informalities: Claim 12 (line 1) is grammatically incorrect, and should recite "as set forth in claim 1…" .

Claim 13 is objected to because of the following informalities: Claim 13 (line 1) is grammatically incorrect, and should recite "test for determining…" .

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 5, 6, 9-21, and 24-26 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

According to the *Interim Guidance for Determining Subject Matter Eligibility for Process Claims in View of Bilski v. Kappos* (75 FR 43922 at 43927 (27 July 2010)), factors that weigh against the eligibility of a process under 35 U.S.C. 101 include: (i) No recitation of a machine or transformation (either expressed or inherent); (ii) Insufficient recitation of a machine or transformation (e.g. a general recitation of a machine that it covers any machine capable of performing the claimed method steps, or a recitation of the machine that is tangentially related to the performance of the steps or merely involves insignificant activity (e.g. data gathering); (iii) The claim is not directed to an application of a law of nature; and (iv) The claim is merely a statement of a general concept (e.g. abstract mathematical concepts or algorithms). It is noted that where the machine or transformation test (i.e. M-or-T test) is not met, analysis is extended to determine whether the claims read on an abstract idea. The prohibition on patenting abstract

ideas has two distinct aspects: (1) when an abstract concept has no claimed practical application, it is not patentable; (2) while an abstract concept may have a practical application, a claim reciting an algorithm or abstract idea can state statutory subject matter only if it is embodied in, operates on, transforms, or otherwise is tied to another class of statutory subject matter under 35 U.S.C. §101 (i.e. a machine, manufacture, or composition of matter). (See In re Comiskey, Fed. Cir., No. 2006-1286, 9/20/07; Gottschalk v. Benson, 409 U.S. 63, 175 USPQ 673, 1972).

In the instant case, the claims are directed to methods for determining a classifier, as in claims 1, 15, and 19, a diagnostic test for determining whether a subject has a pathology, as in claims 13 and 18, and a genetic optimization method, as in claim 21.

Regarding claims 1, 15, and 19, the steps are directed to producing a generation of chromosome populations, computationally genetically evolving the genes, and selecting a classifier. None of the recited steps are expressly or inherently tied to a specific computer or other particular machine. Factors weighing against eligibility under 35 U.S.C. 101 include no recitation of a machine or transformation (expressed or implicit). While the claims recite "computationally" genetically evolving genes, there is no expressed recitation of a computer. Therefore this recitation of "computationally" does not "give life, meaning, and vitality to the claim" (see MPEP 2111.02).

Additionally, the claimed method does not transform (either explicitly or inherently) any particular physical article; e.g. by requiring that a particular physical assay is performed.

Regarding claims 13 and 18, the steps are directed to classifying measurements using diagnostic classifiers. None of the recited steps are expressly or inherently tied to a specific computer. Factors weighing against eligibility under 35 U.S.C. 101 include no recitation of a

machine or transformation (expressed or implicit). Additionally, the claimed method does not transform (either explicitly or inherently) any particular physical article; e.g. by requiring that a particular physical assay is performed. Regarding claim 14, the claim recites using measurements data **obtained from** a microarray and a mass spectrogram, thereby limiting the type of data for analysis in the method. However, claim 14 does not actually recite steps of performing a microarray assay or spectrography, and thus does not recite either a step of transforming a sample nor a step which is tied to a machine.

Regarding claim 21, the steps are directed to computationally genetically evolving the genes, employing fitness criteria, and selecting an optimized chromosome. None of the recited steps are expressly or inherently tied to a computer. Factors weighing against eligibility under 35 U.S.C. 101 include no recitation of a machine or transformation (expressed or implicit). While the claims recite "computationally" genetically evolving genes, there is no expressed recitation of a tie to a specific computer. Therefore this recitation of "computationally" does not "give life, meaning, and vitality to the claim" (see MPEP 2111.02). Additionally, the claimed method does not transform (either explicitly or inherently) any particular physical article; e.g. by requiring that a particular physical assay is performed.

For the above reasons, the claims are wholly directed to an abstract idea, and therefore are directed to non-statutory subject matter under 35 U.S.C. 101.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5, 6, 9, 10, 13, 14, 15, 17, 18, 19, 20, 21, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ooi et al. (Bioinformatics, 2003, Vol. 19, No. 1, p.37-44), in view of Chtioui et al. (J. Sci. Food Agric., 1998; IDS filed 08/07/2006).

Claims 1, 15, and 19 are directed to a method for determining a classifier. For purposes of examination, the critical limitations of the claims are interpreted as follows. The claims require producing a first generation chromosome population. Each chromosome has (i) a selected

number of genes specifying a sub-set of associated measurements; e.g. spots on a microarray (in light of the Specification on page 3), and (ii) an expressed sub-set-size gene having a value distinguishing expressed and unexpressed genes; e.g. an expression level or a binary value corresponding to genes on a microarray (in light of the Specification on pages 3, 10, and 11). The claims also require genetically evolving genes of the chromosomes to a fitness criterion evaluated without reference to unexpressed genes, to produce successive generation populations. The claims result in selecting a classifier that uses the sub-set of associated measurements specified by the expressed genes.

Ooi teaches genetic algorithms applied to the analysis of gene expression data. The genetic algorithm (GA) is based on the selection of the best individuals for reproduction. In particular, the process requires producing a chromosome string comprising genes (i.e. sub-sets), wherein a plurality of chromosomes form a population. See page 39, Col. 1, Algorithm Section. Each chromosome is associated with an ordered set of genes and a particular parameter (i.e. set of measurements); see page 39, Col. 1, ¶4, and Fig. 2. The process of genetically evolving chromosomes is described; see page 39, Col. 1, wherein genes are selected for mating based on a fitness criterion. These genes undergo mating by applying genetic operators to produce successive chromosome populations; see page 39, Col. 1 and Col. 2. This process is repeated until a predictor set of genes with the best fitness is obtained; see at least pages 39, Col. 2 and Fig. 2, which shows selecting a classifier based on a sub-set of associated fitness measurements and replacement of genes with improved fitness. Ooi also shows this entire process applied to gene expression data. In particular, microarray gene expression data sets are disclosed; see page 38, Col. 2. Several different values are described that can be used to distinguish the expressed

genes; e.g. intensity ratio values and index values; see page 38, Col. 2. Empty spots (i.e. unexpressed genes) on the microarray are excluded from the genetic evolution process; see page 38, Col. 2, which shows evaluation without reference to unexpressed genes. Ooi also describes a classifier selection procedure using gene expression data obtained from tumor samples; page 39-40, MLHD Classifier section, wherein Cy5/Cy3 ratios correlate to concentrations of fluorescent markers. The genetic algorithm of Ooi is also applied to a cancer study. More specifically, a data set comprising 14 classes of tumors is classified using the GA; see page 43, Col. 1, which shows using a medical diagnostic classifier for classification into positive and negative groups, since the results are associated with an error rate (i.e. 18% error), which implies 82% positive classification). Ooi discloses mutation rates of genes as high as 0.02%; see Table 1.

Ooi does not teach an expressed gene having a value distinguishing expressed and unexpressed genes of the chromosome, as in claims 1, 15, and 19.

Ooi does not teach an expressed gene containing an ordinal position value, as in claim 2.

Ooi does not teach filling genes of the offspring with gene values common to both parent chromosomes, as in claim 5, or occasionally varying the ordering of the common gene values in offspring, as in claim 6.

Ooi does not teach a mutation rate for the selective mutating of the gene value that are unique to one or the other of the parent chromosomes that is greater than 5%, as in claim 16.

Chtioui teaches methods of feature selection based on genetic algorithms. In particular, pages 79 discusses the genetic algorithm in detail and describes steps for producing a first generation chromosome population (#1, #2), genetically evolving the population respective to a fitness criterion (#3 through #7), and selecting a parameter (i.e. classifier)(#1). Chtioui

exemplifies binary chromosomes with values 0 and 1 used for crossover in evolving populations; e.g. see page 79, Col. 2, which meets claim language for genes having an ordinal position value distinguishing expressed and unexpressed genes of the chromosome, as the binary values represent the presence/absence of genes in a sequence. Each child receives one segment of bits from each parent; see page 79, Col. 2, which shows filling offspring with gene values common to both parent chromosomes. Crossover and mutations are performed; see page 79, col. 2, which shows randomly altering values of each chromosome.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used values distinguishing expressed and unexpressed genes of the chromosome, as taught by Chtioui, in the method of Ooi, since Ooi also teaches crossover and suggests the use of binary classification methods; see page 40, Col. 2, ¶4. The motivation would have been to compare classifier performance by comparing predictor gene sets discovered by different methods, as suggested by Ooi; see page 40, Col. 2, ¶4.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used values an ordinal position value, filling genes of the offspring with gene values common to both parent chromosomes, and occasionally varying the ordering of the common gene values in offspring, as taught by Chtioui, in the method of Ooi, since Ooi also teaches a genetic evolving process based on crossover and mutation of genes with predictable results. The motivation would have been to avoid premature convergence to improve population diversity, as suggested by Chtioui; see page 79, Col. 2.

It would have been obvious for one of ordinary skill in the art at the time of the instant invention to have provided a predictable variation of the step for selectively mutating genes, such

as limiting it to provide a mutation rate that is greater than 5%, with a reasonable expectation of success, in view of the prior art of Ooi, who shows that mutation rate is a design parameter of genetic algorithms, and predictably calculates mutation rates of genes up to 0.02%; see page 39, Col. 2, page 41, Col. 1, and Table 1, and in view of the rationale for a *prima facie* case of obviousness provided by the Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1395-97 (2007). See also MPEP 2143. In this case, the rationale would have been to explore methods for improving genetic algorithm performance based on variations of known design incentives, such as using higher mutation rates, since these variations are predictable to one of ordinary skill in the art. For these reasons, the instant claims do not recite any new element or new function or unpredictable result.

Claims 11, 12, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ooi et al. (Bioinformatics, 2003, Vol. 19, No. 1, p.37-44), in view of Chtioui et al. (J. Sci. Food Agric., 1998; IDS filed 08/07/2006), as applied to claims 1, 2, 5, 6, 9, 10, 13, 14, 15, 17, 18, 19, 20, 21, 24, and 25, above, and further in view of Liu et al. (Evolutionary Computation, 2002, 12-17 May 2002, pages: 297 – 302).

Ooi and Chtioui make obvious a method for determining a classifier, as set forth above.

Ooi and Chtioui do not teach introducing a selected level of noise into values of measurements of the measured subjects, as in claims 11 and 26.

Ooi and Chtioui do not teach randomly or pseudo randomly splitting a set of measured subjects into training groups and test groups before producing successive generation

chromosome populations, as in claim 12. It is noted that splitting a set of measured subjects into training groups and test groups before producing successive generations is interpreted as step of cross-validation, in light of the specification; see page 18.

Liu teaches a method for selecting informative genes using an evolutionary algorithm. In particular, Liu describes the addition of noise into measurement data at a number of different points; see page 297, Col. 2. Liu also describes a validation process wherein training data is randomly shuffled into two subsets, one for constructing a classifier and one for evaluating the classifier; see page 298, col. 2.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have introduced noise into values of measurement data, as taught by Lui, prior to any of the successive generation steps taught in the method made obvious by Ooi and Chtioui, since Ooi already shows the presence of noise in gene expression data; see page 41, col. 1. The motivation would have been to test the performance of simple standard deviation filters to improve fitness, for example, as suggested by Ooi on page 41, Col. 1.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have randomly split a set of measured subjects into training groups and test groups before producing successive generation chromosome populations, in the method made obvious by Ooi and Chtioui, in view of Liu, who teaches a validation process wherein training data is randomly shuffled into two subsets, one for constructing a classifier and one for evaluating the classifier; see page 298, col. 2. Additionally, Ooi teaches cross-validation prior to each evolutionary step, and suggests other cross-over strategies with predictable results; see page 41, col. 1. In each case, the motivation would have been to apply known cross-validation techniques

to obtain an optimal set of classifiers, as suggested by Liu; see page 298, col. 2.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pablo S. Whaley

Patent Examiner

Art Unit 1631

/PW/

/Marjorie Moran/

Supervisory Patent Examiner, Art Unit 1631